THE SYNTHESIS OF COMPOUNDS RELATED TO HEXESTROL

BY

GEORGE PETER MUELLER, III

B. Sc., University of Nebraska, 1940
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THE SYNTHESIS OF COMPOUNDS RELATED TO HEXESTROL

Hexestrol, or *meso*-3,4-*bis*(*p*-hydroxyphenyl)-hexane is a synthetic product possessing estrogenic activity of the same order as the synthetic product diethylstilbestrol, *trans*-4,4'-dihydroxy-α,β-diethylstilbene, and the naturally occurring hormones, estrone (theelin) and estradiol. Since the discovery of its dimethyl ether among the demethylation products of anethole,[1] a number of syntheses have been devised for this useful compound, of which Földi and Fodor's pyrolysis of the reduced ketazine of *p*-methoxypropiophenone[2] and Kharasch and Kleiman's coupling of anethole hydrobromide under the influence of a Grignard reagent and cobaltous chloride[3] have given the most promising results. The yields of hexestrol by these methods were about forty per cent.

The preparation of this compound in another manner was accomplished by the condensation of 3,4-dichlorohexane[4] with anisole in the presence of anhydrous aluminum chloride. The dichlorohexane was found to be very resistant to the action of the catalyst, and the optimum conditions for the condensation required heating the reactants in petroleum ether at 95° for several hours. The crude products from the reaction were methylated and finally yielded one per cent of hexestrol dimethyl ether.

A large number of compounds with structures similar to that of hexestrol have appeared in the literature. The cyclic analogue, 1,2-*bis*(*p*-hydroxyphenyl)-cyclohexane or *cyclohexestrol*, had not been reported.

The first attempt to prepare this compound involved the condensations of phenol and of anisole with cyclohexene oxide, 1,2-dihydroxycyclohexane and 1,2-dichlorocyclohexane in the presence of hydrogen fluoride, boron fluoride and anhydrous aluminum chloride.

Studies of similar condensations have been recorded,

Kursanoff[5] having obtained from the condensation of benzene with chlorocyclohexane and 1,2-dichlorocyclohexane a compound melting at 171°, which he designated as 1,2-diphenylcyclohexane. However, despite recurring reports of this compound obtained from other sources,[6, 7, 8] Nenitzescu and Curcaneanu,[9] and others[10] have proved that Kursanoff's compound was 1,4-diphenylcyclohexane and that an even larger quantity of 1,3-diphenylcyclohexane is formed in the reaction.

The condensations in which phenol was used yielded only *p*-cyclohexylphenol and intractable resins. The reactions with anisole, of which that with 1,2-dichlorocyclohexane in the presence of aluminum chloride gave the best yield of high-boiling materials, produced *p*-cyclohexylphenyl methyl ether, 1,3-*bis*-(*p*-methoxyphenyl)-cyclohexane, m.p. 104°, as well as an oily isomer, and 4,4″-dimethoxy-*m*-terphenyl, m.p. 198°. Both cyclohexane derivatives were dehydrogenated in the presence of palladium on charcoal to yield the terphenyl; thus, hydrogen exchange in the presence of the aluminum chloride accounted for the occurrence of *p*-cyclohexylphenyl methyl ether and 4,4″-dimethoxy-*m*-terphenyl. The crystalline cyclohexane and the terphenyl were demethylated, the phenolic compounds were characterized and their diacetates prepared.

4,4″-Dihydroxy-*m*-terphenyl was oxidized with alkaline potassium permanganate, the solution evaporated to dryness and the residue fused with resorcinol in the presence of concentrated sulphuric acid. The fluorescence and color of a dilute alkaline solution of the fusion mixture was identical with that obtained by similar treatment of isophthalic acid. 1,3-*bis*(*p*-Hydroxyphenyl)-cyclohexane was dehydrogenated in the presence of the palladium catalyst and reduced with zinc dust to give *m*-terphenyl.

The structure of 4,4″-dimethoxy-*m*-terphenyl was originally indicated by the elimination of other possibilities after the synthesis of 4′,4″-dimethoxy-*o*-terphenyl, m.p. 106°, and of 4,4″-dimethoxy-*p*-terphenyl, m.p. 275°.

4′,4″-Diamino-*o*-terphenyl, prepared according to the

method of Allen and Pingert,[11] was tetrazotized and treated with steam to yield 4′,4″-dihydroxy-*o*-terphenyl, m.p. 230° which was methylated.

4,4″-Dinitro-*p*-terphenyl was prepared by the directions of France, Heilbron and Hey,[12] reduced to give 4,4″diamino-*p*-terphenyl, m.p. 244°, and converted through the tetrazonium salt to 4,4″-dihydroxy-*p*-terphenyl, m.p. 375°, which was methylated.

The demethylated products, both pure and crude, from the condensations of cyclohexene derivatives with anisole were tested for estrogenic activity in spayed rats and were found to be inactive. 1,3-*bis*(*p*-Hydroxyphenyl)-cyclohexane, m.p. 229°, was also inactive androgenically.

The synthesis of cyclohexestrol dimethylether was accomplished through the following series of reactions:

1,4-Dianisoylbutane was prepared according to the directions given by Fuson, Kuykendall and Wilhelm.[13] This diketone was hydrogenated in the presence of Raney nickel or copper chromite catalyst or reduced with aluminum isopropoxide to give a mixture of diastereoisomeric 1,6-*bis*(*p*-methoxyphenyl)-1,6-dihydroxyhexanes which, when treated with thionyl chloride, gave 1,6-*bis*(*p*-methoxyphenyl)-1,6-dichlorohexane, m.p. 112°, with decomposition, and when treated with hydrogen bromide gave 1,6-*bis*(*p*-methoxyphenyl)-1,6-dibromohexane, m.p. 103°, with decomposition.

The action of phenylmagnesium bromide and cobaltous chloride on the dibromohexane eliminated bromine from the molecule and gave rise to a mixture of oils from which a crystalline compound was isolated having the composition of 1,2-*bis*(*p*-methoxyphenyl)-cyclohexane, m.p. 72°. The action of sodium on the dibromohexane appeared to give the same product, but it could not be purified from higher-melting impurities. Magnesium metal and sodium amide in liquid ammonia were ineffective in closing the cyclohexane ring.

A synthesis of cyclohexestrol that was proposed involved a diene condensation in which 2,3-*bis*(*p*-methoxyphenyl)-1,3-butadiene was to condense with a dieneophile to yield a cyclo-

hexene derivative having the *p*-methoxyphenyl substituents in the 1,2 position. Toward the preparation of the suitable diene, *p*-methoxyacetophenone was electrolytically reduced to the corresponding pinacol*. Two diastereoisomers of this pinacol, melting at 168° and 123°, respectively, were isolated from the crude reduction mixture. The higher-melting form was also obtained by reduction with aluminum amalgam in moist ether. Dehydration with acetyl chloride, used successfully by Fraser[14] on the pinacol obtained from acetophenone, resulted in rearrangement of the pinacol. The pinacol could not be esterified in alkaline solution. In acid solution it immediately rearranged to give 3,3-*bis*(*p*-methoxyphenyl)-2-butanone, m.p. 72°; oxime, m.p. 194°. Fusion of the ketone with potassium hydroxide yielded 1,1-*bis*(*p*-methoxyphenyl)-ethane, m.p. 72°.[15] The Beckmann rearrangement of the oxime yielded 1, 1-*bis*(p-methoxyphenyl)-ethene.[16] Presumably, 1-acetamino-1,1-*bis*(*p*-methoxyphenyl)-ethane was the intermediate in this reaction but was hydrolyzed and lost ammonia to yield the ethylene. The iodoform reaction as modified by Fuson and Tullock[17] was unsuccessful with the original pinacolone.

Another proposed synthesis of cyclohexestrol by the diene method required the preparation of 1,2-*bis*(*p*-methoxyphenyl)-1,3-butadiene. The preparation of this butadiene was thought possible by the addition of acetylene to desoxyanisoin to form *p*-methoxybenzyl-*p*-methoxyphenylethynyl carbinol, which could then be partially hydrogenated and dehydrated to the diene. Though the addition of acetylene to the carbonyl group has been found generally to be successful,[18,19,20,21] the reaction did not proceed with desoxyanisoin.

An attempt to prepare cyclohexestrol was made by forcing a Grignard reaction between *p*-methoxyphenylmagnesium bromide and 1,2-dibromocyclohexane. From the reaction were obtained 4,4′-dimethoxybiphenyl and 4,4″-dimethoxy-*p*-terphenyl. The course taken by the reaction was assumed to be that of Grignard exchange between the reagent and 1,2-dibro-

* These reductions were carried out by Howard D. Marshall and Herman Kerfman under the direction of Professor Sherlock Swann of the Department of Chemistry.

mocyclohexane, coupling of *p*-methoxyphenylmagnesium bromide with the *p*-methoxyphenyl bromide formed to give 4,4′-dimethoxybiphenyl, and demethoxylation of the latter by the excess Grignard reagent to yield methoxymagnesium bromide and 4,4″-dimethoxy-*p*-terphenyl. This hypothesis was proved to be correct when the reaction of *p*-methoxyphenylmagnesium bromide and 4,4′-dimethoxybiphenyl in dibutyl ether at 140° was found to yield four per cent of the theoretical amount of 4,4″-dimethoxy-*p*-terphenyl. Evidence of the presence of higher polyphenyls was also observed. Fuson and Speck[22] have reported similar replacements of methoxyl groups by Grignard reagents in aryl ketones, where there would appear to be a chance for 1,4-addition of the reagent to the ketone. There was no such opportunity in the 4,4′-dimethoxybiphenyl molecule, and so the reaction was unique. It indicates a possible new synthesis of polyaryls.

Certain of the hormones found in the adrenal cortex bear close resemblance to the estrogenic hormones but have as a distinguishing characteristic a hydroxyacetyl group in the 17-position on the cyclopentanophenanthrene nucleus. The introduction of such a substituent into the hexestrol molecule might prove valuable in modifying its physiological activity.

Toward the introduction of the hydroxyacetyl residue, hexestrol dimethylether was treated with chloroacetyl chloride in the presence of aluminum chloride. The reaction was not successful. 3,4-*bis*(*p*-Chloroacetoxyphenyl)-hexane, m.p. 146°, was prepared from hexestrol and chloroacetyl chloride and subjected to the action of aluminum chloride at 140°. A red or yellow compound was isolated which contained no halogen and gave evidence of dehydration, possibly with formation of a coumaranone ring.

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VITA

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